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REVIEW

Traditional Ethnomedical and Ethnobotanical Applications and Uses of Piper Nigrum

Argyrios Periferakis[1,2,3], Lamprini Troumpata[1], Konstantinos Periferakis[2,4], Grigorios-Marios Adalis[1], Aristodemos-Theodoros Periferakis[1,3], Spyrangelos Georgatos-Garcia[5,6], Calina Maier[7,8], Andrei C. Costache[9], Dragos N. Garofil[10,11], Daniel O. Costache[12,13]

1 Department of Physiology, The "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
2 Akadimia of Ancient Greek and Traditional Chinese Medicine, Athens, Greece
3 Elkyda, Research & Education Centre of Charismatheia, Athens, Greece
4 Pan-Hellenic Organization of Educational Programs (P.O.E.P.), Athens, Greece
5 Tilburg Institute for Law, Technology, and Society (TILT), Tilburg University, DE Tilburg, The Netherlands
6 Corvers Greece IKE, Athens, Greece
7 Department of Gynecology, The "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
8 Panait Sirbu Obstetrics and Gynaecology Hospital Bucharest, Bucharest, Romania
9 The "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
10 Department of General Surgery, The "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania
11 Department of General Surgery, "Dr. Carol Davila" Clinical Hospital of Nephrology, Bucharest, Romania
12 Department of Research, "Dr. Carol Davila" University Central Military Emergency Hospital, Bucharest
13 Discipline of Dermatology, The "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania

Correspondence: Argyrios Periferakis, argyrisperiferakis@gmail.com

Abstract: Ethnomedicine and ethnobotany have been at the forefront of current scientific focus. The focus of this review is Piper nigrum, for which there exists a wide host of traditional ethnomedical and ethnobotanical applications, recorded mostly from India and the surrounding regions where black pepper is native. These applications cover a wide range of pathologies, including cardiovascular, pulmonary, gastrointestinal, gynaecological, endocrine, integumentary and neurological, and viral diseases and colds. While some of these applications are confirmed by modern research, the majority have not been tested using modern scientific methods, and perhaps many more applications remain to be documented. Finally, it must be noted that some interesting non-medical applications comprise the application of black pepper, as an insecticide/larvicide, are worth further consideration, especially given the newer policies at a European and international level.

Keywords: *Piper nigrum*; black pepper; ethnomedicine, traditional uses

INTRODUCTION

Herbs and spices have been used for medicinal, preservative, and culinary purposes since antiquity in numerous traditional medicine systems [1-4]. In recent years, there has been an increase in research efforts, dealing both with recording ethnomedical and ethnobotanical practices across different regions, and verifying the reported uses by employing modern analytical and experimental methods [5-8]. The focus of this review is black pepper (*P. nigrum*), which has a long history of culinary history and use.

In Indian culinary tradition, black pepper has been an integral part since about the 2nd millennium BC, and numerous traditional herbal recipes are mentioned by Venkatachalapathi et al. [9]. Many ethnozoological uses of *P. nigrum*, combined with other components, also exist in India [10]. Given that *Piper nigrum* was originally cultivated in India [11], it makes sense that the record of relevant ethnomedicinal and ethnobotanical applications will be rich in this country and in the surrounding regions. Traditional uses of *P. nigrum* are reported from nearby regions as well.

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TRADITIONAL ETHNOBOTANICAL AND ETHNOMEDICINAL APPLICATIONS OF BLACK PEPPER

Applications in Cardiovascular System Pathologies

Regarding cardiovascular pathologies, the fruit of *P. nigrum* is mixed with other ingredients in a powder in the area of Odisha, India, to combat hypertension [17]. Based on in vivo experiments in rats, it was proven that piperine could normalise

hypertension and aortic ring reactivity [62]; therefore, there is at least experimental confirmation of the previous usage. An additional use for cardiovascular pathologies is recorded in the area of Tiruvallur where *P. nigrum* is used in different formulations, along with other plants and herbs, in these uses [16].

Table 1: Traditional ethnomedical and ethnobotanical applications of P. nigrum.

Part of the Plant Used	Country/Region	Type of Ailment	Year	Reference
Cardiovascular Pathologies				
Seeds (used to make a decoction with *Z. officinale* leaves)	Maharashtra, India	Generalised oedema	2006	[12]
Seeds (used to make a paste with leaves of *C. ternatea* L.)	Tamil Nadu, India	Leg swelling	2012	[13]
Seeds (made into paste with other plant parts, and used to make tablets)	Odisha, India	Haemorrhoids	2012	[14]
Fruits	Tamil Nadu, India	Good circulation promotion	2015	[15]
Different parts in various formulations	Tamil Nadu, India	Cardiovascular pathologies	2016	[16]
Fruits (powdered with other ingredients)	Odisha, India	Hypertension	2018	[17]
Respiratory Pathologies				
Seeds (powder for internal administration)	Tamil Nadu, India	Cough	2007	[18]
		Bronchial disorders		
Seeds, fruits	Orissa, India	Cough	2010	[19]
Different parts of the plant (combined with *E. cardamomum*, *A. galanga*, *Z. officinale*, and sugar)	Western Ghats, India	Asthma	2011	[20]
Seeds (powdered added in *V. negundo L.* leaf decoction with honey)	Odisha, India	Cough	2012	[14]
Raw fruits	Kerala, India	Sinusitis	2015	[21]
Seed (powder combined with dried leaf powder of *G. bosvallia*)	Madhya Pradesh, India	Whooping cough	2018	[22]
Gastrointestinal Pathologies				
Leaves (leaf juice is mixed with leaf and root bark powder of *K. grandiflora*, and leaf powder of *C. halicacabum*)	Tamil Nadu, India	General gastric problems	2005	[23]
Seeds (dried and swallowed)	Tamil Nadu, India	Stomach ache	2006	[24]
Seeds (powdered, mixed with root of *P. margaritiferum* Scott)	Odissa, India	Dysentery	2010	[25]
Seeds (powdered, with bark decoction of *P. xylocarpum*)		Infantile diarrhoea		
Fruits (powdered, mixed with *T. dioica* leaf decoction)		Diarrhoea		
Different parts of the plant (combined with different plants)	Western Ghats, India	General gastric problems	2011	[20]
Different parts of the plant	Tamil Nadu, India	General gastric problems	2012	[26]
Fruits (combined with numerous different plants and made into a decoction)	Karnataka, India	Intestinal ulcers	2012	[27]
		Aphthae		
Seeds [combined with *T. asthmatica* (L. f.) Wight &Arn roots, garlic and fruits of *S. cumini*, made into paste]	Karnataka, India	Jaundice	2012	[28]
Fruits (in powder form – oral adm.)	Assam, India			
Seeds (mixed with seeds of *B. roxburghii* and jaggery, made into tablets)	Maharashtra, India			
Fruits (combined with *C. dactylon* and *P. amarus* leaves – subsequently an extract is produced)	Tamil Nadu, India			
Seeds	Assam, India	Indigestion	2013	[29]
Leaves (used to make an infusion)	Misiones, Argentina	Digestive complaints	2014	[30]
Fruits (macerated with other plants to make pills)	Jhenaidah, Bangladesh	Ulcer	2014	[31]
Fruits (powder for oral administration)	Kerala, India	Stomach ache,	2014	[32]
		Indigestion		
Raw fruit	Kerala, India	Vomiting	2015	[21]
Seeds (crushed and mixed with different ingredients)	Phnom Penh, Cambodia	Liver pathologies	2017	[33]

Different parts (combined with *C. diococcum*, *C. aromatica*, *P. nigrum*, and *P. betle* and salt)	South Western Ghats, India	Stomachache	2018	[9]
Fever, General Anti-Inflammatory Actions, Musculoskeletal Complaints and Stomatological Pathologies				
Fruit (powdered with *A. vasica* Nees)	Karnataka, India	Fever	2005	[34]
Seeds (mixed with powder of *H. isora* L., *A. sativum* rhizome, and gingelly oil, and boiled)	Tamil Nadu, India	Earache	2007	[18]
Different parts of the plant (combined with *A. vasica* and honey to form a paste)	Western Ghats, India	Headache, earache	2011	[20]
Different parts of the plant (combined with *E. cardamomum*, *A. galanga*, *Z. officinale*, and sugar)		Headache		
Fruits (mixed and macerated with other plant parts and then made into a paste)	Jessore & Narail, Bangladesh	Bone fractures	2011	[35]
Seeds (paste with *Caesalpinia bonduc* L. and honey)	Odisha, India	Fever	2012	[14]
Seeds (powdered and applied with salt)	Tamil Nadu, India	Toothache	2012	[26]
Fruits (combined with different plant parts, ground and boiled in water)	Karnataka, India	Gingival wounds	2012	[27]
Seeds [with macerated leaves of *E. indica* (L.) Gaertn]	Rajshahi & Nawabganj, Bangladesh	Spinal cord pain	2013	[36]
Seeds [powdered with macerated roots of *L. aspera* (Willd.) Link]		Headache due to fever or dog bite		
Seeds (powdered with crushed bark of *D. peregrina* L.)		Chest pain (various causes)		
Seeds (powdered with macerated whole *S. cordata* to create a paste)		Abscess		
Fruit (decoction or infusion)	Batan, Philippines	Toothache	2013	[37]
Seeds	Assam, India	Pain (of various causes)	2013	[29]
Fruit (powdered in *C. serratum* decoction/root extract)	Bengal & Andhra Pradesh, India	Fever	2014	[38]
Fruits	Tamil Nadu, India	Throat pain	2015	[15]
Seeds (paste)	Kerala, India	Fever, cuts, wounds	2015	[21]
Seeds/fruits (as part of a multi-plant mixture)	High Atlas, Morocco	Musculoskeletal complaints	2016	[39]
Seeds/fruit (powdered)	Khushab, Pakistan	Malarial fever and body pain	2017	[40]
Seeds (combined with animal and plant parts)	Chota Nagpur Plateau, India	Headache	2017	[41]
Fruit (powdered in *O. sanctum* L. leaf decoction with palmgur)	India (different regions)	Fever	2018	[42]
Different parts (combined with *C. caudata*, *O. sanctum*, *C. monophyla*, and *P. nigrum*, combined with milk and honey)	South Western Ghats	Fever	2018	[9]
Gynaecological and Reproductive System Pathologies				
Fruits (mixed with *C. pareira* L.)	Assam, India	Post-partum birth control	1982	[43]
Fruits	Assam, India	Post-partum pain	2008	[44]
		Lactation difficulties		
Seeds [combined with a paste of *T. cordifolia* (Willd.)]	Eastern Rajasthan, India	Leucorrhoea	2010	[45]
Fruit (powdered mixed with the root juice of *A. aspera*)	Narail & Jessore, Bangladesh	Menstrual pain	2011	[35]
Fruits (powdered and added to a macerated mixture of different components to make pills)		Prolapse of uterus		
Seeds (macerated with roots of *P. daemia* Forsk., and made into pills)	Rajshahi district, Bangladesh	Menstrual irregularities	2012	[46]
Seeds	Assam, India	Post-labour ailments	2013	[29]
Fruit (powdered, mixed with *P. hydropiper* leaf paste and made into pills)	Jhenaidah, Bangladesh	Menstrual pain	2014	[31]
Seeds (ground with newly-sprouted *N. arbor-tristis* leaves to make pills)	Jammu, India	Menorrhagia	2014	[47]

Seeds (powdered with leaves of *P. granatum* and mixed with water; a filtrate is then produced)		Leucorrhoea		
Seeds (powdered with eight spoons of *S. indicum* seeds and jaggery and boiled in water)		Oligomenorrhea		
Seeds (powdered with two spoons of *S. indicum* seeds and jaggery and boiled in water)		Hypomenorrhoea		
Fruit (macerated)	Andaman & Nicobar islands, India	Lactation difficulties	2015	[48]
Seeds/fruits (as part of a multi-plant mixture)	High Atlas, Morocco	General gynaecological complaints	2016	[39]
Different parts (combined with *A. excelsa*, *C. aromatica*, *P. nigrum* and *P. betle,* and coconut oil)	South Western Ghats, India	Menstrual irregularities	2018	[9]
Neurological Pathologies				
Seeds [powdered and added into the flower extract of *Calotropis procera* (Aiton)]	Uttarakhand, India	Epilepsy	2013	[49]
Leave extract	Thailand	Insomnia	2014	[50]
Seeds (made into pills combined with *L. interrupta* roots)	Chota Nagpur Plateau, India	Epilepsy	2017	[41]
Seeds (made into pills combined with other plants)				
Seeds (mixed with honey)		Insomnia		
Endocrine Pathologies				
Fruits (crashed with fruits of *C. nymphaeifolia* Vent.)	Jessore, Bangladesh	Goiter	2011	[51]
Seeds (added to a juice of three leaves of *M. charantia* L.)	Mauritius	Type 2 diabetes mellitus	2014	[52]
Fruits (used to make a decoction)	Songkhla, Thailand	Diabetic neuropathy	2015	[53]
Different parts (with *A. marmelos*, *C. aromatica*, *P. betle*, coconut oil and honey to make a herbal preparation)	South Western Ghats, India	Diabetes mellitus	2018	[9]
Ailments of Viral Cause and Common Cold				
Different parts of the plant (combined with other plants into a paste)	Shimoga, India	Common cold	2010	[54]
Seeds, fruits	Orissa, India	Common cold	2010	[19]
Different parts of the plant (combined with *A. vasica* and honey to form a paste)	Western Ghats, India	Common cold	2011	[20]
Seeds (powdered, with dried ginger and palm sugar made into a coffee-like preparation)	Tamil Nadu, India	Common cold	2012	[26]
Seeds (powdered, added with salt in an omelette)				
Fruits (mixed with multiple plant components in a complex preparation)	Rajshahi, Bangladesh	Influenza	2012	[55]
Seed (powder with roots of *S. virginianum* L.)	Rajshahi & Nawabganj, Bangladesh	Chickenpox	2013	[36]
Leaves (mixed with ginger and honey)	Kodagu, India	Common cold	2013	[56]
Fruits (powdered for oral administration)	Tamil Nadu, India	Viral hepatitis	2014	[57]
Seeds (used to make a decoction)	South Western Ghats, India	Common cold	2018	[9]
Different parts (combined with *E. variegata*, *O. tenuiflorum*, *P. nigrum* and *P. betle*, and honey)				
Treatment of Parasitic Infections				
Fruits (crushed and mixed with ghee)	Assam, India	Scabies	2006	[58]
Seeds (boiled in milk and water)	Eastern Rajasthan, India	Malaria	2010	[45]
Leaves (crushed, applied either alone or in combination with other components)		Ringworm		
Fruits	Karnataka, India	Scabies	2014	[59]
Treatment of Bites				
Seeds (powder for internal administration)	Tamil Nadu, India	Snake bite	2007	[18]
Seeds (powdered and mixed with butter)	Eastern Rajasthan, India	Snake bite	2010	[45]
Fruits (macerated with leaves of *A. indica*)	Narail & Jessore, Bangladesh	Snake bite	2011	[35]

Fruits (made into a paste with lime juice and the roots of *L. indica*, and *C. medica*)	Karnataka, India	Snake bite	2012	[27]
Fruits (ground with root of *D. metel*)	Jhenaidah, Bangladesh	Dog bite	2014	[31]
Flowers (mixed with ghee)	Various regions, India	Snake bite	2017	[60]
Different parts (combined with *C. diococcum*, *C. aromatica*, *P. nigrum*, and *P. betle* and salt)	South Western Ghats, India	Dog bite	2018	[9]
Different parts (combined with *T. indica*, C. *aromatica*, *P. betle* and coconut oil)		Scorpion bite		
Treatment of Skin Diseases				
Seeds (powdered and added to crushed, soaked and filtered *P. murex* L., mixed with sugar candy)	Eastern Rajasthan, India	Various skin diseases	2010	[45]
Seeds (macerated with part plants and honey to make pills)	Jessore, Bangladesh	Various skin diseases	2011	[51]
Fruits (ground with minerals, camphor and other plant parts)	Karnataka, India	Foot xeroderma	2012	[27]
Fruits (made into a paste with other plant parts and coconut oil, and boiled)		Gangrene		
Seeds (powder mixed with betel leaf paste)	Hyderabad, India	Eczema	2013	[61]
Fruits	Karnataka, India	Dandruff	2014	[59]
		Pruritus		
		Eczema		
		Bed sores		
		Boils		

Another application regarding the cardiovascular system concerns the use of seeds of *P. nigrum*, combined with roots of *Rawolfia serpentina*, dried rhizome of *Zingiber officinale*, and seeds of *Piper longum*, all in paste form, which are used to make tablets; these are then administered orally for 10 to 15 days to treat haemorrhoids [14]. In Tamil Nadu, India, the fruit of *P. nigrum* is used to promote a state of overall health and good circulation [15].

Many ethnomedical and ethnobotanical applications are concerned with swelling and the presence of oedema, either localised or generalised. In many cases, a pathology of cardiovascular nature is the cause of oedema formation [63]. In the district of Amravati, India, a decoction made from the leaves of *Zingiber officinale* and P. *nigrum* seeds is taken once daily for 5 days to treat generalised swelling [12]. A paste made from leaves of *Clitoria ternatea* L. and *P. nigrum* seeds is applied on swollen legs in Sivagangai district, India [13].

Applications in Respiratory System Pathologies

In the region of Western Ghats, the Kani healers combine *Elettaria cardamomum*, *Alpinia galanga*, and *Zingiber officinale*, combined with sugar, to treat headache and asthma [20]. In the region of Kerala, the raw fruit of black pepper is used to treat sinusitis [21], while the seed and fruit are used to treat cough [19], in Orissa, India. In Odisha, a decoction of black pepper seeds and *Vitex negundo* L. leaves mixed with honey is taken orally to relieve cough [14].

In Madhya Pradesh, India, a preparation consisting of the dried leaf powder of *Glossocardia bosvallia* and the powder of *P. nigrum* seeds is administered to patients with whooping cough [22]. This pathology is caused by *Bordetella pertussis*, a bacterial pathogen whose presence has been recorded in human populations for centuries. Its importance is currently considered to be of endemic proportions despite the existence of an appropriate vaccine [64].

Applications in Gastrointestinal System Pathologies

For general gastric problems, in the region of Western Ghats, India, *P. nigrum* is combined with *Tephrosia purpurea*, *Carmona retusa*, and *Piper hymenophyllum* and used by the Kani healers [20]. In the Nadar community of the Atoor village, in Tamil Nadu, black pepper is used to treat gastric complaints of various causes [26]. In another area of Tamil Nadu, gastric complaints are treated with a mixture of *P. nigrum* leaf juice, leaf powder, and root bark powder of *Kleinia grandiflora*, and powder from *Cardiospermum halicacabum* leaves [23].

The powder of *Piper nigrum* fruits is administered in the Silent Valley of Tamil Nadu, to treat stomach ache and indigestion [32]. In other parts of India, the dried seeds are taken orally [24]. An infusion made from *P. nigrum* leaves is used to treat digestive problems by Polish migrants in Misiones, Argentina [30].

In Assam, the seeds of the plant are given to treat indigestion [29]. The raw fruit of *P. nigrum* is given to treat vomiting in regions of Kerala [21]. In the case of a stomach ache, the same preparation as for dog bites is used in some regions of the SW Ghats, India [9]. In Bargarh, the powder of seeds and fruits is combined with different parts of different parts, in various formulations, to treat infantile diarrhoea, in infants and adults, and dysentery [65].

Quite a number of formulation exist regarding the treatment of jaundice; for example, in the region of Karnataka, *P. nigrum* seeds are mixed with roots of *Tylophora asthmatica* L., garlic and fruits of *Syzygium cumini*; in the region of Assam, the fruits of black pepper are used in powder form; in the region of Maharashtra, its seeds are mixed with jaggery and *Balanotis roxburghii* seeds; in the region of and Tamil Nadu, its fruits are is combined with ground leaves of Cynodon dactylon and Phyllanthus amarus and an extract is produced [28]. This last use is also mentioned by [66], based on the earlier research of [67]. Regarding liver pathologies, a paste containing crushed black pepper seeds and four other ingredients is used by the Khmer traditional healers in Cambodia [33].

For the treatment of ulcers, in the Jhenaidah district of Bangladesh, leaves of *Polygonum hydropiper*, nutmeg, a fruit of *Terminalia chebula*, *Carum carvi*, and young leaves of *Cynodon dactylon* are mixed with *Piper nigrum*, and macerated to prepare a pill mixture [31]. Another therapy, this time specifically for intestinal ulcers, comes from the Uttara Kannada district of India, where the fruits of *P. nigrum* are used in combination with about 10 different plant parts and made into a water decoction with jaggery to be orally administered; the same preparation is used in the case of aphthae.

Antipyretic and General Anti-Inflammatory Applications and Musculoskeletal Complaints

In the village of the Shimoga district, Karnataka, India, black pepper powder is mixed into the leaf paste of *Adhatoda vasica* Nees; this formulation is then made into pills for oral administration [34]. In other parts of India, black pepper powder is added to *Clerodendrum serratum* decoctions or aqueous root extracts, which are then administered once per day orally, for three days [38]. The Kani healers of Western Ghats have a preparation containing *P. nigrum*, honey, and parts of *Alpinia vasica*, which they use to cure headaches and earaches; the same tribe uses another formulation to treat headaches as well as asthma [20]. In the region of Assam, seeds of black pepper are used to treat pains in different parts of the body, from different causes [29]. The fruits of the plant are used to treat throat pain in the area of Tamil Nadu [15].

In different regions of India, *P. nigrum* and palmgur are added to the leaf decoction of *Ocimum sanctum* L. [42]. A similar preparation is used in the SW Ghats [9]. In the region of Kerala, the paste of the seeds is known to have an anti-inflammatory effect in cases of fever, cuts, and wounds [21]. In the district of Odisha, *Caesalpinia bonduc* L. is made into a paste along with seeds of *P. nigrum*, and taken with honey to cure fever [14]. A complex mixture of plant and animal parts, containing black pepper seeds, is made into pills and administered orally once per day, for 10 days, to treat headache in the Chota Nagpur Plateau [41].

For the treatment of earache, in the area of Tamil Nadu, the fruit powder of *Helicteres isora* L. is boiled with *P. nigrum* seeds, *A. sativum* rhizome, and gingelly oil; the resulting fluid is applied locally in the affected area [18].

In Pakistan, black pepper seeds are also known for their antipyretic properties, and also for their action against fever-induced body pain, when the fever is of malarial origin [40].

In Bangladesh, there are many different anti-inflammatory uses of black pepper reported, such as a paste made from black pepper seeds and macerated leaves of *Eleusine indica* (L.) Gaertn applied once daily for 21 days, in cases of pain in the spinal cord. In the case of severe headache due to fever or dog bites, the macerated roots of non-flowering *Leucas aspera* (Willd.) Link is mixed with 10-15 powdered seeds of *Piper nigrum* L., and prepared for oral administration. As a form of abscess treatment, a paste made from macerated *Sida cordata* (Burm.f.) Borss.Waalk. is mixed with black pepper seed powder and applied around the abscess. Finally, in the case of chest pain of various causes, seed powder is mixed with crushed bark of *Diospyros peregrina* L., and applied locally, particularly in the cases where the chest pain is caused by gout [36].

In other regions of Bangladesh, in Jessore and Narail, some of the leaves of *Morus indica* are mixed with rhizomes of *Zingiber officinale*, 20 fruits of *Piper nigrum*, and 25-30 drops of oil prepared from seeds of *Brassica campestris*; this mixture is then macerated thoroughly and applied as a thick paste over the affected area. A bandage is then placed over the applied paste and changed, along with the mixture, every 7 days [35]. Another preparation, containing *P. nigrum* as part of a multi-plant mixture called Msahan, is used in the High Atlas region of Morocco [39], to treat general musculoskeletal complaints.

In the Philippines, a decoction or infusion of black pepper is used to cure a toothache [37]. In India, again, to treat toothache, in the Atoor village, powdered pepper and salt are applied in dental cavities [26]. Still on the subject of oral-related pathologies, a complex infusion is made, containing many different plant parts along with *P. nigrum fruits*, which is then used, when lukewarm, to gargle, when there are gingival complaints [27].

Applications in Gynaecological and Reproductive System Pathologies

One ethnomedicinal preparation containing *P. nigrum*, as part of a multi-plant mix, comes from the High Atlas region of Morocco, and is named Msahan; it is used generally to treat various types of gynaecological complaints [39]. For post-labour ailments, the seeds of *P. nigrum* are used in Assam, India [29]; specifically for post-partum pain, the fruit of *P. nigrum* is administered in Tinsukia district, India [44]. In the same regions, there also exist some ethnomedical recipes for post-partum birth control [68]; for example, in some cases, the fruits of *P. nigrum* are used, along with pieces of *Cissampelos pareira* L., and the duration of administration depends on the desired length of contraception [43].

Menorrhagia, i.e., heavy menstrual bleeding, is defined as a bleeding of over 80 mL per menstrual cycle, and usually occurs as a result of uterine abnormalities, endometrial abnormalities, ovulation, or coagulation disorders; the treatments and their effectiveness vary depending on the primary cause [69]. In Udhampur, India, the newly sprouted leaves of *Nyctanthes arbor-tristis* are ground along with Piper nigrum seeds to make 2 g tablets, which are administered twice per day for two weeks [47].

Oligomenorrhoea is another type of menstrual cycle disorder, where the menstrual cycle lasts more than 35 days and less than 90 days [70], or the total menstrual cycles per year are between 5 and 7 [71]. It is a problem of increasing importance in recent years [72]. The usual causes are associated with endocrine disorders [73]. In Udhampur, India, eight spoons of *Sesamum indicum* seeds and the powder of *Piper nigrum* seeds and jaggery are boiled in water until the volume is reduced by half; the produced liquid is taken twice a day, for 15 days, before the due date of each successive period [47]. A similar treatment is used in cases of hypomenorrhea [47], which is defined as a menstrual bleeding of 1-2 days or when the amount of blood is too low, even in the context of a normal duration of menstruation [74].

Leucorrhoea, or fluor albus, may be physiological in women, during menstruation, or pathological; in this latter case, a foul smell, colour changes, and other symptoms such as itching and a burning sensation are present. Usually, pathological leucorrhoea is associated with a urogenital infection [75]. There are two recorded ethnobotanical treatments for leucorrhoea containing *P. nigrum* in India. The first one is from the region where a paste of *Tinospora cordifolia* (Willd.) is combined with five seeds of black pepper and administered once in the morning [45]. In the district of Udhampur, India, the leaves of *Punica granatum* are crushed, the powder from *P. nigrum* seeds is added, and then both are mixed with water; a filtrate is then produced, which is consumed twice a day [47].

Another common gynaecological problem is menstrual pain, i.e., primary dysmenorrhoea, which affects both young and adult females, especially from a quality-of-life perspective; treatment remains mostly symptomatologic [76]. The Kavirajes tribe in Bangladesh mixes one fruit of *P. nigrum* with the juice of one root of *Achyranthes aspera*, and gives it to affected females on an empty stomach once only [35]. In the same country, in the district of Jhenaidah, a paste obtained from the leaves of *Polygonum hydropiper* is mixed with 1 powdered fruit of *Piper nigrum*, to make pills that are taken thrice per day for 2-3 days [31].

Menstrual cycle irregularities are a relatively common problem in many populations, affecting between 5% and over 30% of females of reproductive age [77]. There exists several modifiable and non-modifiable risk factors associated with irregular menstruation [78,79]; regardless, irregular menstruation is associated with some pathologies and a decrease in quality of life (80). In the SW Ghats, India, *Ailanthus excelsa*, *Curcuma aromatica*, *Piper nigrum*, and *Piper betle* are combined with coconut oil and made into a herbal remedy for the cure of menstrual problems [9]. In the Rajshahi district, Bangladesh, the roots of *Pergularia daemia* Forsk. are macerated with 2-3 seeds of *Piper nigrum L.*, and then pills are made, which are taken thrice daily [46].

Uterine prolapse, one of the manifestations of pelvic organ prolapse in women, affects over 5% of most female population worldwide [81-83]. In Bangladesh, in the Jessore and Narail districts, the roots of *Abutilon indicum*, *Glycosmis pentaphylla*, *Eleusine indica*, and *Amaranthus spinosus*, are mixed together and macerated, and then sugar and 21 powdered black pepper fruits are added and 42 pills are prepared from this mixture; 1 pill is taken daily for 14 days [35].

In the case of lactation difficulties, the macerated fruit of *P. nigrum* is orally administered by the healers of the tribes of Andaman and Nicobar islands, India [48]. In Tinsukia district, the fruit of *Piper nigrum* is used to increase breast milk production [44].

Applications in Neurological Problems

Of particular note are the mentions of *P. nigrum* in the context of traditional Indian medicinal approaches to epilepsy. The seed of the plant, when combined with either *Laportea interrupta* roots or the stem of *Cissus repanda*, and the roots of *Leea macrophylla*, and *Mucuna pruriens*, is used to treat epilepsy in the Chota Nagpur Plateau, in India. Also in the same area, for the treatment of insomnia, *P. nigrum* is mixed with fresh honey from the Indian honey bee (*Apis cerana indica*), and applied inside the nose [41]. In the region of Uttarakhand, powdered seeds of *P. nigrum* are mixed with the flower extract of *Calotropis procera* (Aiton) [49]. Meanwhile, in Thailand, the leaf extract from *P. nigrum*, which has a demonstrably high melatonin content, is traditionally used to treat insomnia [50].

Applications in Endocrine Pathologies

In Jessore, Bangladesh, the crushed fruits of P. nigrum are combined with crushed fruits of *Colocasia nymphaeifolia* Vent. and taken twice daily for 7 days, to treat goiter [51]. Goiter can be attributed to a number of causes, the most common of them being iodine deficiency; the worldwide prevalence of goiter is quite high [84].

For the treatment of diabetes mellitus, in the Walayar valley, India, different parts of *Aegle marmelos*, *Curcuma aromatica*, *Piper nigrum*, and *Piper betle* are combined with coconut oil and honey to make the relevant herbal medicine [9]. Specifically for type 2 diabetes mellitus, a juice from three leaves of *Momordica charantia* L. and *Piper nigrum*, to be consumed once a week, is administered [52]. For the treatment of one of the complications of diabetes, diabetic neuropathy-associated numbness, a decoction made from the fruits of black pepper in *Songkhla province*, Thailand, its administration has a proven hypoglycaemic effect in rats [85].

Applications in Ailments of Viral Cause and Colds

In Bangladesh, the roots of *Solanum virginianum* L. are powdered and mixed with black pepper seed powder to cure chickenpox [36], an extremely contagious viral disease caused by the Varicella-Zoster virus [86]. In Tamil Nadu, India, the powder from *Piper nigrum* fruits is administered orally in cases of viral hepatitis [57]; viral hepatitis is attributable in most cases to the five different hepatitis viruses [87].

In the district of Shimoga, India, to treat the common cold, *P. nigrum* Linn. and *Allium sativum* Linn. are combined with plants of the Caesalpiniaceae spp. and made into a paste, which is taken orally for 3-4 days [54]. In Tirunelveli hills of Western Ghats, India, *P.*

nigrum is combined with *Alpinia vasica* and honey, and the resulting paste is used by Kani traditional healers against the common cold, but also against headache, and earache [20]. In the Karnataka region of India, the leaves of *P. nigrum* are pounded and mixed with ginger and honey; they are taken for 3-5 days orally to treat the common cold and associated cough [56]. The fruits and seeds of *Piper nigrum* are used to treat the common cold in Orissa, India [19]. Seed powder is swallowed to treat cough and bronchial disorders in Coimbatore district, India [18].

In the Kanyakumari district, Tamil Nadu, India, black pepper is used in a number of formulations for different ailments. Regarding the treatment of the common cold, black pepper, dried ginger, and palm sugar are mixed along with water to prepare a coffee-like drink, which is then administered to patients; omelettes are also made with powdered pepper and salt and given to such patients [26].

In the Walayar valley of India, a decoction made from seeds of *P. nigrum* is used as a treatment for cough and cold; another more complex herbal preparation containing black pepper, from the same area, also exists [9].

For the treatment of influenza, caused by the viruses of the Orthomyxoviridae family [88] in Rajshahi district, Bangladesh, a complex preparation comprising 12 fruits of black pepper, along with a number of different plant parts, is used [55].

Applications in the Treatment of Parasitic Infections

There are reports that if black pepper seeds are boiled in milk and water and administered orally, once in the morning for a period of 4 to 5 days, the multiplication of malarial parasites is decreased and splenomegaly regresses [45]. In the case of ringworm infection, the crushed leaves of the plant are rubbed directly onto the parasite; in other cases, the leaves are crushed and mixed with cow milk or mustard oil or crushed with bulblets of garlic and mixed with lemon juice is applied on ringworm to affect a complete cure [45]. Both of these antiparasitic applications are common in the region of Eastern Rajasthan, India.

Scabies is increasingly being diagnosed, at least in certain countries [89]; it is caused by the host-specific human scabies mite (Sarcoptes scabiei varietas hominis). While the infection is not life-threatening on its own, bacterial superinfections are common [90]. In the Central Western Ghats region, India, the fruits of black pepper are used to treat scabies [59]. In Assam, the crushed fruits of *P. nigrum* are mixed with ghee and the resulting product is orally administered [58].

Applications in the Treatment of Bites

In Eastern Rajasthan, seed powder mixed with butter is given orally against snake bite [45]. A similar preparation exists for snake-bitten animals in Uttaranchal, India [91]. The same recipe is also known in other areas of India, while the paste of *P. nigrum* flowers with ghee is administered orally for the same purpose [60]. In the region of Karnataka, the fruits of *P. nigrum* along with the root of *Citrus medica* and *Leea indica*, are used to make a paste, mixed with lime juice, which can be both applied externally and swallowed, in cases of snake bite [27]. The powder of black pepper seeds is administered internally to counteract the effects of snake poison, in the *Coimbatore district*, India [18]. In Bangladesh, several leaves of *Aristolochia indica* are mixed with 2-3 fruits of *Piper nigrum*, and are then macerated; finally, a juice is obtained which is administered immediately [35].

Finally, for the treatment of dog bites, in the district of Jhenaidah, fruits of *P. nigrum* are mixed with roots of Datura metel and ground. The resulting ground mass is administered orally as soon as possible [31]. In the SW Ghats, India, *Canthium diacocum* is combined with *Curcuma aromatica*, *Piper nigrum*, and *Piper betle*, and salt, to make a preparation used in the case of dog bites [9]. In the same region, *P. nigrum* is combined with *Tamarindus indica*, *Curcuma aromatica*, *Piper betle*, and coconut oil to treat scorpion bites [9].

Applications in the Treatment of Skin Diseases

Crushed *Pedalium murex* L. is soaked in water overnight, filtered the next morning, mixed with sugar candy and seed powder of black pepper, and then administered orally as a treatment for various skin diseases in Eastern Rajasthan, India [45]. Again, for skin diseases generically, seeds of *P. nigrum* are macerated with roots of *Rauwolfia serpentina* (L.) Benth. ex Kurz and rhizomes of *Zingiber officinale* Roscoe, with honey added afterwards; in this way, pills are made which are administered daily for 3 weeks, for prophylaxis, in Jessore, Bangladesh [51]. In Central Western Ghats, India, the fruits of *P. nigrum* are used to treat dandruff, pruritus, eczema, bed sores, and boils [59]. Regarding eczema, a different traditional cure, comprising the powder of black pepper seeds and betel leaf paste, applied daily, is used in Hyderabad, India [61].

For foot xeroderma, the fruit of *P. nigrum* along with the seed and bark of *Semecarpus anacardium*, the fruit of *Vernonia anthelmintica*, the flower bud of *Syzygium aromaticum*, and the rhizome of *Curcuma longa* are ground with copper sulphate, camphor tablets, and boiled in cow's ghee, grease, and paraffin; they are then applied externally [27]. A rather more complex preparation with more than 10 plant parts, comprising also the fruits of *P. nigrum*, is made into a paste with coconut oil and boiled; it is applied externally after it has cooled [27].

DISCUSSION

Research in phytochemistry has revealed the remarkable therapeutic properties of black pepper. While its antimicrobial, antiparasitic, and antiviral effects are well-known, many other beneficial properties of black pepper extracts have been researched thoroughly, including its anti-inflammatory, anticonvulsant, and analgesic properties [92-94]. It seems that it may be possible to use it, in an adjuvant role, in a mode similar to that of capsaicin [95,96]; perhaps its integration in 3D-printed biomaterials [97-99] as a potent antimicrobial would represent another promising application. Related to inflammation, based on a review of available data, concluded

that the terpenes present in black pepper, in combination with taurine, can have an anti-atherogenic effect, with parallel antimicrobial and metabolic benefits [100]. Given the extensive number of ethnomedical and ethnobotanical data, as presented in this text, and also discussed by various authors [11,101,102], it can be observed that a number of them are corroborated by recent experimental data, while the effectiveness of others is still to be determined. For example, the addition of piperine in the treatment of jaundice or of various gynecological problems warrants further research. Cutaneous applications may show effectiveness due to the potential of piperine to modulate cellular and humoral components in the skin, as well as interact with inflammatory pathways, in a similar manner as other phytochemicals [103-106]. Other traditional applications of piperine in neurological problems, namely epilepsy, may be of importance, given the prevalence and severity of certain epileptic syndromes [107-109]. In addition to testing the effectiveness and applicability of reported uses, a sustained effort should be made to complete the recording of such uses across different cultures, where black pepper has been used extensively for centuries.

Combination of Black Pepper with Acupuncture

Given that capsaicin has been proven an effective anti-bacterial [110] anti-inflammatory agent when applied at acupuncture points [95], a promising research direction seems to be the application of black pepper cream in similar points, alone or combined with capsaicin and other phytochemicals. Currently, there exist protocols for acupuncture in diabetic patients, with the acupuncture points Zusanli (ST36), Shenshu (BL23), Sanyinjiao (SP6), Yishu (EX-B3), and Zhongwan (CV12) being the most studied; protocols for diabetic neuropathy, one of the main complications, also exist and are presented in detail by Ma et al. [111]. The available evidence indicates that acupuncture is useful as an adjuvant therapy in diabetic patients [112], although the design and completion of more long-term trials is considered necessary.

Continuing on the potential combinations of acupuncture with the traditional applications of black pepper, it is noted that based on the research from the area of Bangladesh, black pepper is applied as a paste in case of gout-related chest pain [36]. Regarding gout and gouty arthritis, there are currently available acupuncture protocols [113-115], while based on a recent case study, it is possible to use acupuncture and moxibustion in the context of renal insufficiency [116]. Notably, recent research has demonstrated the renoprotective potential of piperine in the case of hyperuricemic nephropathy [117].

Black Pepper in Metabolic Diseases

Another interesting research direction concerns the effect of black pepper on glucose and lipid regulation. Regarding glycaemic control, in rats, black pepper extract was found capable of reducing blood glucose [85,118]. Inhibition of aldose reductase was noted by [119]; aldose reductase is the enzyme most associated with the complications of diabetes [120,121]. More recent research results in vitro are also in favour of the hypoglycaemic activity of black pepper [122,123].

These findings are important in the context of increasing incidence and prevalence and complications of diabetes mellitus [124-132], the associated mortality [133-135], the adverse effects of antidiabetic drugs [136-138], and the burden of disease [139-141]. Moreover, intestinal dysbiosis, specifically with Enterobacteriaceae and Candida species, was found to be a risk factor for diabetes mellitus type 1 [131]; piperine is effective against such pathogens and thus it could, hopefully, be used in a dual antiglycemic-antimicrobial role.

In rats, the addition of black pepper to their diet had a hypolipidemic effect [142,143]. A more recent successful experiment, performed by administering the methanolic leaf extract of *Piper guineense*, a species of pepper native to West Africa, in female diabetic rats, indicates that it can be used in the management of diabetic patients, with no adverse biochemical effects [144]. A leaf extract from the same plant species has demonstrated properties beneficial for glycaemic control in vitro [145]. In rats, immunohistochemical and histological data support the antidiabetic potential of black pepper in combination with other compounds [146], although further research is required on the matter. Such experiments are in accordance with a recent trend in evaluating the potential beneficial effects of spices in diabetic patients [147].

Hyperlipidaemia is associated with diabetes mellitus [148,149] and is, in all contexts, a risk factor for morbidity and mortality [150-152]. Therefore, the administration of black pepper extracts in general and piperine in particular, in high enough – but tolerable – concentrations, will benefit glycaemic and lipidaemic control both in diabetic and non-diabetic patients. Based on evidence on the interplay between obesity and inflammation [153], and taking into account the evidence in favour of piperine application in cases of obesity and inflammation, it is reasonable to consider the potential of a two-pronged effect of piperine administration in such cases.

Anticarcinogenic Effect of Piperine

It appears that there is a significant corpus of data in favour of anticarcinogenic effects of piperine [11,154-157]. When taking into account the different pathways, like molecular and metabolic, implicated in carcinogenesis (e.g., [158-169]), it is clear that there are numerous potential pathways upon which piperine may act to exert its anticarcinogenic potential. We would like to highlight the potential effectiveness of piperine in the treatment of hepatocellular carcinoma [170], the most prevalent form of liver cancer [171], and other phytochemicals were already shown to be good candidates [172,173]; this raises the possibility of combining piperine and the already used somatostatin analogues [174,175], to increase their effectiveness, in this and other forms of cancers. Piperine could be combined with a number of other natural compounds, which have a known anticarcinogenic potential [168,176] to maximize their efficiency; furthermore, taking into account the potential associations of certain pathogens with cancer [177,178], it could function both in an anticarcinogenic and anti-inflammatory role. The association of diabetes and colorectal cancer [179] also opens new avenues for piperine applications with a dual effect.

Non-medical properties of P. nigrum

Black pepper also has some notable ethnomedical veterinary uses, with the fruit being included in pastes or creams or infusions, to treat blotting [180], constipation, skin infections [181], various ailments [55], and helminthic infections [182] in animals. Other uses are also reported in the literature [183-187].

Perhaps more important are the applications of *P. nigrum* as a component of insecticides and larvicides. Early evidence of the insecticidal and larvicidal potential of black pepper, piperine, and its derivatives was provided by a number of experiments [188-190]. A later experiment by [191], documented the toxicity of black pepper extract on the rice weevil, *Sitophilus oryzae* (L.). It was previously observed that when exposed to white pepper, all the *Anopheles larvae* died [192], and it was then that the potential of this plant as an anti-malarial agent was first realised. A mix of ground black pepper and piperine was found to be very effective against a number of larvae of the same species [193]. Crucially, the mode of action of black pepper extracts is different from that of pyrethroids, meaning that potential resistance to the latter will not affect the action of the former; they both exhibit a marked potential for synergistic action between them [194]. Even more importantly, black pepper extracts and piperine are not toxic to other organisms and do not persist in the environment [195,196]. Piperine itself has been shown to be effective against the larvae of *Aedes aegypti*, the vector of the yellow fever and Dengue fever viruses [197,198]. Regarding a less dangerous species of mosquito, *Culex pipiens*, the common house mosquito, the study of [199] demonstrated that piperine-based dienehydrazide derivatives were more effective than piperine itself or Deltamethrin. Another study investigated the potency of *P. nigrum* against ant species, along with that of other plant extracts; the results were promising, revealing a viable alternative [200].

Given the adverse impacts of larvicides and insecticides in both the environment and human health [201-203], and existing threats to the biodiversity of different environments [204-207], efforts to incorporate natural compounds into insecticides and larvicides should intensify. The increased effectiveness of such compounds is important both in the context of agriculture [208-210] and, perhaps more importantly, in the context of the insect-borne diseases [211-213].

In response to the aforementioned health and safety concerns, both the European Union (EU) and the United Nations (UN) (https://sdgs.un.org/goals) have implemented measures to regulate and reduce reliance on hazardous chemicals, while exploring natural alternatives. The EU's regulatory framework (e.g., Regulation (EC) No 1107/2009 [214], Regulation (EU) 2022/1438 [215], Directive 2009/128/EC [216]), multilateral treaties like the Rotterdam Convention [217,218] and the Stockholm Convention [219,220], and research and development (R&D) programs strongly emphasize promoting directly or indirectly innovation in plant-based substances. The EU also provides funding opportunities through Horizon Europe [221], the largest research and innovation program supporting projects in sustainable agriculture, biodiversity, and green technologies.

Additionally, global initiatives such as the International Plant Protection Convention (IPPC) [222], the intergovernmental treaty that aims to protect the world's plants, agricultural products and natural resources from plant pests and the FAO (Food and Agriculture Organization of the United Nations) Guidelines on Pesticide Management [223,224] provide the necessary foundation for the establishment of national legislation and policies for pest and pesticides management, with the potential inclusion of more favourable conditions for biopesticides. Other organizations, such as OECD (https://www.oecd.org/), have dealt with the topic of biopesticides while there are countries worldwide with dedicated frameworks on the matter, like the US EPA (www.epa.gov/pesticides/biopesticides) and China's Plan for Green and Sustainable Agricultural Development [225], encouraging biological control methods to reduce synthetic pesticide use.

CONCLUSION

Piperine and black pepper extracts exhibit ethnomedical and ethnobotanical applications, which should be explored further, with the aim of developing novel therapeutic solutions for a number of different pathologies. Future research should concentrate on elucidating the effectiveness of such applications in in vivo settings, using modern methods, and exploring the potential of increasing the active concentration via the application of novel delivery methods.

Finally, the non-medical applications of piperine and black pepper in general are promising in the field of insecticides/larvicide development, in accordance with the new directives of the EU and of other nations.

Conflicts of interest and sources of funding

The authors declare no conflict of interest. No artificial intelligence automatically generated text was inserted in this manuscript, and no image was previously published in another journal or is under consideration of being published elsewhere. This research received no external funding.

Authors' contribution

Conceptualization AP, ATP, AFG, DOC and CC; methodology AP, AFG, DOC and CC; validation AP, MP, DOC, and CC; formal analysis AP, LT, KP, ATP, GMA, AFG and CC; investigation AP, LT, KP, ATP, GMA, SPG, AFG and DLC; resources AFG and DLC; data curation DOC; writing—original draft preparation AP, ATP, SPG, AFG; writing—review and editing AP, ATP, DOC, and CC; supervision AP, MP, DOC and CC; project administration AP, AFG, and DLC. All authors have read and agreed to the published version of the manuscript elaboration

Ethics approval and consent to participate

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